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Human cancer: epidemiology and environmental causes

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9

Cultural factors: tobacco

9.1 Introduction

Tobacco, particularly cigarette smoking, accounts for more cancer deaths than all other known factors. Cancers caused by smoking include those of the lung, oral cavity, pharynx, larynx, esophagus, urinary bladder, renal pelvis and pancreas (IARC, 1986). The most important of these is lung cancer. Whether any excess cancers of the stomach, liver, kidney and cervix are attributable to smoking is still uncertain. As the cigarette habit expands, especially in developing countries, tobacco-associated cancer deaths are increasing. Consumption of smokeless tobacco is also growing in several parts of the world, often on the assumption that it is not dangerous. Several studies suggest that side-stream tobacco smoke, which exposes bystanders to other people's tobacco smoke (passive smoking) may constitute a cancer risk (IARC, 1986; O'Neill *et al.*, 1987).

The literature on tobacco cancer issues has been extensively reviewed (IARC, 1985; 1986; 1987; Zaridze & Peto, 1986; O'Neill *et al.*, 1987). The object of the present chapter is to provide a brief introduction to certain general issues, the role of tobacco usage being described in more detail under specific cancer sites.

9.2 History

Although tobacco smoking was quickly regarded as a vice following its introduction in Europe, the carcinogenic properties of tobacco tar were first demonstrated experimentally by Roffo in the late 1920s. However, it was not until the early 1940s that epidemiological evidence appeared from Germany (Müller, 1939) indicating that smoking was a lung carcinogen. Later, following the work of Wynder and Graham (1950) in the US, and Doll and Hill (1950) in the UK, a large number of

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studies were undertaken which confirmed the causal relationship, not only with lung but which also indicated that other sites could also be affected (IARC, 1986). There was, however, initial resistance in accepting the carcinogenic role of cigarette smoking. First, the habit did not become widespread until after World War I and the long latent period between starting smoking and lung cancer development meant that the lung cancer epidemic was not recognized until the 1950s. Further, in the earlier period, pathologists frequently misdiagnosed lung tumors which were considered rare (Willis, 1948). An important factor was the unwillingness of many experimentally oriented scientists to accept a pleasurable habit as dangerous and to recognize the strength and relevance of epidemiological studies which they tended to disparage. At the Oxford meeting in 1950 (Historical Introduction), the association was doubted by such an astute observer as Clemmesen, who had found no increase in Denmark despite its excellent cancer registry. As further studies appeared and it was realized that the induction period could be over 20 years, the discrepancy between contemporaneous tobacco consumption figures and cancer rates became explicable.

It was not, however, until the report of the Royal College of Physicians in the UK (1962) and later, that of the Surgeon General in the US (1964), that the causal role of tobacco was fully accepted and the issue of tobacco cancer became of concern to public health and legislative bodies. None the less, tobacco sales continued to rise and governments refused to increase taxes. The tobacco industry remained antagonistic, dismissing the epidemiological data as being 'only statistical', and continued advertising in the media, thus succeeding in maintaining doubts among the public regarding the causal association. In the 1960s, the industry began to introduce filter or low-tar cigarettes. Such cigarettes became popular among the general public, who clearly regarded them as less hazardous, although the term 'safer' was never used by the industry which has continued to maintain that cigarettes were not dangerous.

Later, as concern regarding environmental contamination by chemicals increased, there was a tendency to try and transfer blame for the lung cancer increase to air pollution, although the problem had been extensively examined in the 1940s and 1950s. As recently as 1989, a prominent newspaper reported inaccurately that the Environmental Protection Agency (EPA) regarded radon exposure as the number one cause of lung cancer.

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Production and use

Tobacco for smoking comes in several forms (IARC, 1986), of which the following are the most important:

(a) Cigarettes, which are very commonly used in Europe and North America, and increasingly elsewhere.
(b) Cigars, all of which are made from air-cured and fermented tobacco, and, while used all over the world, are in decline in many American and European countries. On occasion, as in Thailand, additives may be incorporated.
(c) Pipe tobacco.
(d) Bidi, used extensively in India, contains a relatively small amount of locally grown tobacco, usually sun-dried. The tobacco is usually rolled in the leaf of the temburni tree and sometimes in tobacco leaves. Size may vary considerably. They produce a smaller volume of smoke than cigarettes.
(e) Kreteks are cigarettes that are widely manufactured in Indonesia. 'Stick bruise' is the cigarette grown in Papua, New Guinea and leads to a long large cigarette known as a stick.
(f) Reverse smoking, i.e. With the glowing end of a cigarette inside the mouth results in cancer of the hard palate in parts of India, Venezuela and Sardinia.

There are a variety of other home-made smoking materials prepared from home-grown tobacco in China, Zambia, Pakistan, etc. which have their own characteristics and names and will not be itemized here. As a generalization, any smoke from tobacco-containing products increases the risk of malignancy. The methods of harvesting and curing various types of tobacco differ radically: there is both flue-cured tobacco where individual leaves are cut as they ripen, and air-cured tobacco which is used for cigar filler. In flue-curing, tobacco is dried entirely by artificial heat in such a way to prevent smoke from coming into contact with the leaf; in air-curing, little or no artificial heat is applied. At present, China, the USA, India and Brazil are the leading producers.

Blond and dark tobacco are typically used in Europe and Latin America respectively and appear different in their impact on human cancer (Chapter 33).

Smoking and public health considerations

Although cigarette manufacture began in the mid-nineteenth century, e.g. papirossi in Russia, it was only with their mass production prior to World War I that the habit expanded enormously. Free

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distribution of cigarettes to soldiers during World War I introduced many to smoking.

The causal association of cigarette smoking with lung cancer was the first example of the power of modern epidemiology to identify a cause of cancer involving the general population, despite the long latent period. Further, it has been a unique example in illustrating the success of public health intervention outside the work-place in preventing the disease.

Estimates of tobacco smoking in different countries generally reveal rising consumption in most countries from the 1920s to the 1960s (IARC, 1986). Thus, from 1923 there was approximately a six-fold increase in the number of cigarettes consumed per adult in Australia and a five-fold increase in Austria. Overall figures, however, disguise very significant changes that have occurred in many countries in recent years. Thus today, the above figures require modification as there have been changes in the sex ratios of smokers. Females have increased smoking, whereas the prevalence has decreased in many groups of males. Further, there are marked age, class and socio-economic differences in the use and discontinuation of the habit. The use of filtered cigarettes has widely increased in many countries, yet those with high-tar yields of 35 to 55 mg per cigarette remain on the market especially in third world countries.

In the United States and the United Kingdom, cigarettes have a greater effect than pipe or cigar tobacco possibly because inhalation of pipe or cigar smoke is less pleasant. However, those who inhale significantly from cigar tobacco have higher lung cancer rates than cigarette smokers.

Active agents in tobacco smoking

Cigarette smoke is a highly complex mixture of chemicals, over 3000 having been identified. Most studies have concentrated on tar and nicotine yields. Generally, changes in cigarette design since 1955 have been reflected in a decline of average tar and nicotine levels. Thus, in the US, as in the UK, the average tar yield has fallen from just under 40 mg per cigarette to about 13 mg of tar.

This chemical complexity has made it difficult to identify any individual agent as the predominant carcinogenic factor. However, considerable progress has been made in identifying the fractions that are most likely to contain the active carcinogens relevant to humans.

An enormous mass of data has now been collected on the chemical compounds present in tobacco (Table 9.1), and the effects of tobacco smoke and tobacco tar on experimental animals (IARC, 1986; O'Neill *et al.*, 1987; Hecht & Hoffman, 1989). Despite difficulties in reproducing

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Table 9.1. *Biologically active agents in mainstream smoke*[a]

Smoke constituent	Conc./cigarette	Biological effect[b]
Total particulate matter	15–40 mg	T, HC
Carbon monoxide	10–23 mg	T
Nicotine	1.0–2.5 mg	T
Acetaldehyde	0.5–1.2 mg	CT
Acetone	100–250 μg	CT
NO_x	50–600 μg	T
Formic acid	80–600 μg	CT
Hydrogen cyanide	400–500 μg	CT, T
Catechol	140–500 μg	CoC
Ammonia	50–130 μg	T
Benzene	20–50 μg	HC
Acrolein	50–100 μg	CT
Acrylonitrile	3.5–15.0 μg	C
Phenol	60–140 μg	TP
Formaldehyde	5–100 μg	C
Carbazole	1 μg	C?
2-Nitropropane	0.2–2.2 μg	C
N'-Nitrosonornicotine	120–3700 ng	C
4-(Methylnitrosamino)1-(3-pyridyl)-1-butanone	120–950 ng	C
N'-Nitrosonabasine	120 ng	C?
N-Nitrosodiethanolamine	0–40 ng	C
N-Nitrosophyrrolidine	2–110 ng	C
N-Nitrosodimethylamine	2–180 ng	C
N-Nitrosomethylethylamine	0.1–40 ng	C
N-Nitrosodiethylamine	0.1–28 ng	C
N-Nitrosodi-n-propylamine	0–1 ng	C
N-Nitrosodi-n-butylamine	0–3 ng	C
N-Nitrosopiperidine	0–9 ng	C
N-Nitrosopyrrolidine	2–42 ng	C
Hydrazine	24–43 ng	C
Urethane	20–38 ng	C
Vinyl chloride	1.3–16 ng	HC
Benz[*a*]anthracene	40–50 ng	C
Benzo[*a*]pyrene	10–50 ng	C
5-Methylchrysene	0.6 ng	C
Dibenz[*a,j*]acridine	3–10 ng	C
2-Naphthylamine	4.3–27 ng	HC
4-Aminobiphenyl	2.4–4.6 ng	HC
2-Toluidine	30–160 ng	C
Polonium-210	0.03–1.0 pCi	

[a] Quantitative data refer to non-filter cigarettes.
[b] Abbreviations: T, toxic-agent; HC, human carcinogen; CT, ciliatoxic agent; CoC, co-carcinogen; TP, tumor promoter; C, animal carcinogen.
(After Hoffmann and Wynder, 1986.)

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human exposure, considerable data has been obtained on the carcinogenicity of whole smoke in its gaseous phase. Tumors have been produced in a range of animals either through inhalation or by direct painting of cigarette smoke condensate. Tobacco smoke has shown both initiating and promoting activities which are consistent with the epidemiological studies.

Measuring exposure

Early studies relating to lung cancer were based on patient recall of smoking habits. This proved more than adequate in identifying the impact. However, where low levels of exposure, as in passive smoking, are involved, other techniques must be used. Exposure to tobacco smoke can be determined by measuring chemical or biological markers of tobacco smoke constituents or by measuring intake indirectly from butts or puffing patterns. At present, the only acceptable biochemical markers that can distinguish passively exposed non-smokers from non-exposed individuals are measurements of nicotine in urine and saliva and cotinine in urine, saliva and plasma (Chapter 5). There is some evidence that the prevalence of chromosomal aberrations in the blood cells of smokers is a function of the number and the tar yield of cigarettes smoked.

Individual susceptibility

Approximately 80% of the tar inhaled from mainstream cigarettes is deposited in the respiratory tract, the majority in the tracheobronchial region. However, there is wide individual variation in the amount of tar deposited dependent on pattern of smoke inhalation and exhalation. Studies of host factors that influence susceptibility show that smokers with lung cancer are of the extensive debrisoquine metabolizer phenotype and also have high levels of aryl-hydrocarbon hydroxylase (AHH) (Chapter 17). However, the impact of such genetically determined differences in lung and bladder cancer as well as other sites has not been fully established.

Interaction with other factors

In evaluating cancer and its relation to tobacco, the importance of mixed exposures should be taken into consideration. Thus, both smoking and alcohol are causes of cancer of the tongue, mouth, pharynx, larynx and cancer of the esophagus. Both act independently but are partly synergistic. Attribution of risk is complicated since many smokers tend also to consume excess alcohol.

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There appears to be a definitive synergistic impact of radon and asbestos (Chapter 5).

In contrast, it has also been suggested that smoking may indirectly reduce the incidence of some hormone-dependent cancers, notably of the endometrium, by reducing blood estrogens at menopause, but the 'gain', if any, is trivial compared to the increased risk of lung cancer.

Influence of duration of dose and cessation of smoking

Such relationships have been examined in depth (Peto, 1986). Duration of use is an important consideration when correlating trends in national cigarette consumption, tar per cigarette and cancer incidence in different cultures and at various time periods. In brief, duration of exposure is of greater importance than dose.

If smoking ceases, the annual excess risk remains roughly constant thereafter. This implies that if the annual excess risk after 30 years is about 0.1%, then this annual excess risk may persist indefinitely. This process is not reversed but the risk remains markedly reduced as compared to that of continued smoking. As a practical public health policy, cessation of smoking means that individuals who stop smoking before developing cancer avoid much of the risk.

Cohort effects

As smoking habits among different age-groups vary, reflecting variations in the proportion of persons born at different times who took up the habits, birth cohort analysis of lung cancer incidence and mortality has provided useful information. The original studies by Clemmensen in Denmark clearly identified the impact of cigarette smoking in younger individuals and its impact on cancer induction (IARC, 1986).

Low tar cigarettes

As noted above, substantial reductions in cigarette tar yield have occurred in many countries in recent years due to a combination of public pressure and regulation.

The IARC (1986) working party concluded that:

'(1) Although smokers of "low tar" cigarettes tend to compensate for lower yields of nicotine and perhaps other smoke components, chiefly by changing the manner of smoking, they do not in general compensate fully for lower tar yields.'

'(2) Case-control and cohort studies suggest that prolonged use of non-filter and "high-tar" cigarettes is associated with greater lung cancer risks than prolonged use of filter and "low-tar" cigarettes.'

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'(3) In a few countries, in which smoking had been established for many years, a substantial reduction in mortality from lung cancer has been observed in young and middle-aged men, which is greatest in the youngest age groups. This has occurred at a time when the number of cigarettes smoked by young men in these countries has remained approximately constant. No substantial cause (or cofactor) has so far been identified that offers a plausible explanation for the observed magnitude of the reduction of risk for lung cancer, other than changes in cigarette design which include reduction in tar content.'

Passive smoking

In recent years there has been growing concern regarding the dangers of passive smoking and this is discussed under lung (Chapter 34).

Other cancers have been attributed to passive smoking, including the nasal cavity, brain and a number of other sites. In general, findings are difficult to interpret, especially as a very strong association has not been found in smokers (O'Neill *et al.*, 1987). A limited number of studies have found no clear evidence for an association of cancer in children with parental smoking.

Smoking in developing countries

In view of the different times at which tobacco entered the market, there are significant differences in the present distribution of lung cancer and the prevalence of the habit. Although tobacco consumption has fallen by about 1% per annum in developed countries, it is increasing by 1 to 2% in the developing world. It is inevitable that there will be an enormous impact of smoking in third world countries in future decades which is not reflected in existing cancer rates.

9.3 'Smokeless' tobacco

Tobacco can be taken as snuff (both inhaled and chewed), chewed by itself or with a variety of other ingredients, the best known of which is the betel quid. Tobacco in virtually all of these forms is carcinogenic (Chapters 23, 32 and 33) (Table 9.2).

Snuff inhaled

The snuffs currently used for inhalation in Europe and North America, denoted as dry (Scotch) snuff, comprise powdered tobacco and a variety of additives which blenders keep secret.

Hill in 1761 ascribed nasal cancer to heavy snuff inhalation. Brinton *et al.* (1984) in a case-control study found an increased relative risk (RR) of

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Table 9.2. *Relative risk (RR) for cancers of oral cavity and pharynx associated with use of snuff and smoking by 196 white women in North Carolina.*

	RR	Numbers	
		Cases	Controls
Snuff only	4.2	79	80
Smoking only	2.9	70	101
Snuff and smoking	3.3	11	14
Neither habit	1.0	36	153

(After Winn *et al.*, 1981.)

3.1 for adenocarcinoma of the nasal cavity and sinuses and of 1.9 for squamous cell carcinoma in snuff users in the USA, but the snuff was 'dipped' (see below) rather than inhaled.

In South Africa, the snuffs used by the Bantu comprise tobacco leaves admixed with the ash of aloes (Liliaceae family), oil, lemon juice and variety of herbs. Keen *et al.*, (1955) obtained a history of prolonged and heavy use of these snuffs in 80% of patients with cancer of the maxillary sinus compared to 34% in persons with other sites of cancer.

Snuff 'dipped'

Snuff 'dipping' is the name given in the Southern USA to the placing of snuff between cheek and gum. The highly alkaline 'wet' snuff so deposited is chewed or sucked. Winn *et al.* (1981) found that females in North Carolina with cancers of tongue, gum, floor of mouth, other mouth, oropharynx, hypopharynx showed considerable excess of risk for snuff dippers (Table 9.2).

Investigations on an unexpectedly high level of oral cancer in females in several southern and eastern states (Mason *et al.*, 1975), showed that many women in the textile industry took snuff as smoking was forbidden.

Chewing tobacco

Tobacco, whether cut from a roll or plug, twist, or in the commoner loose-leaf form, is still chewed in parts of the US and elsewhere (Williams & Horm, 1977). A population based case-control study showed, among men, that use of chewing tobacco and snuff was strongly associated with cancers of the gum and mouth, but not of the lip or tongue.

In recent years, tobacco chewing and snuff-dipping habits have

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Table 9.3. *Relative risks, with 95% confidence intervals, for oral leukoplakia associated with use of nass with and without smoking in 1569 men aged 55–69 years in Samarkand region of the Uzbek SSR.*

	Smoking	
	No	Yes
Nass use		
No	1.0	7.8 (4.4–14.2)
Yes	5.6 (3.4–9.5)	11.5 (5.4–24.3)

(After Zaridze *et al.*, 1985.)

increased among high school and college students, especially athletes. Precancerous lesions were found in over 40% (Greer & Poulsen, 1983).

Nass

Use of nass is widespread in Soviet Central Asia, Northern Iran, parts of Pakistan and Afghanistan (Nasswar). Nass is a mixture of variable composition and usually contains tobacco, ash, lime and cotton seed oil. In Afghanistan, cardamom oil and menthol are added.

The habitual use of nass is associated with oral leukoplakia (Zaridze *et al.*, 1985). Relative risks were significantly elevated in nass users and smokers; the combined habits in risk (Table 9.3) seemed to result in an additive effect.

Betel quid

The chewing of betel quid, with or without tobacco, is widespread in the Indian sub-continent, South-East Asia and parts of Oceania. The habit is of great antiquity, tobacco being added form the sixteenth century onwards. The basic quid comprises the leaf of the betel vine (*Piper betle*), sliced or shaved areca nut from the so-called betel palm (*Areca catechu*), and powdered slaked lime to which are added one or more of a wide variety of additives. However, when tobacco (usually of the sun-dried variety) is added to the chew, the risk of oral and, probably oropharyngeal, hypopharyngeal and oesophageal cancer is substantially increased (Orr, 1933; Hirayama, 1966) (Table 9.4).

9.4 Conclusions and public health considerations

Despite clear-cut knowledge of the effects of smoking, and oral use of tobacco for a number of social and economic reasons, comparatively little has been done through governmental regulation to control

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Table 9.4. *Relative risk of oral cancer in chewers and non-chewers in the case-control studies.*

Frequency of chewing	Orr (1933)	Hirayama (1966)
Never	1[a]	1
Occasional	5	8
3–5/day	18	15
5+/day	34	18
Sleeps with quid in mouth	200[a]	63

[a] Risk estimate based on two cases

this habit. The greater part of public health measures have been directed towards education and fostering social pressures against smoking. The possibility that the habit could be made safer, through, for example, the reduction of tars, although not favored in North America, is still considered a potential, if less desirable, alternative in Europe for those who must smoke.

The findings are consistent: oral use of smokeless tobacco, whether prepared industrially or by artisanal means, increases the risk of oral cancer (IARC, 1985).

These habits are far from being esoteric curiosities in that they are widely practised by large numbers of people, possibly as many as 400 million, and give rise to an estimated 100,000 and 50,000 cancers each year in males and females respectively (Parkin *et al.*, 1988) (Chapter 23).

The preparation of snuff and chewing tobacco in the USA is on an industrial scale, some 40 million pounds of snuff being produced in 1980. Estimates of the number of current users of smokeless tobacco range from 7 million to 22 million. In the Orient, however, much of the preparation of the betel quid and its components are at the artisan level and production figures are difficult to obtain.

The tobacco companies, faced with lower sales of cigarettes in the developed countries are now, despite clear evidence of the carcinogenicity of the habit, promoting the use of chewing snuff, the product being sold in the form of sachets for oral use (Cameron, 1985). If the sale of these products, which do not carry any health warning, is allowed to continue the toll of periodontal disease and oral cancer will be high.

For control measures to have a chance of success, the motives underlying adoption of a habit should be understood. Much work has been done in this area for smoking, but very little for the oral use of tobacco.

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Cultura

10.1 Introducti

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